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Substrate binding implications in the X-ray structure of a nicotinamidase from a metagenomic bacteria with biotechnological interest

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NAD+ is a central cofactor that plays important roles in cellular metabolism and energy production in all living cells. Nicotinamidases are essential enzymes for the recycling of nicotinamide into NAD+ in most prokaryotes and most of lower eukaryotes, but not in mammals. These enzymes convert nicotinamide to nicotinic acid and its significance for nicotinamide salvage and for NAD+ homeostasis has stimulated interest in nicotinamidases as possible antibiotic targets. In fact, some of them have pyrazynamidase activity being able to metabolize pyrazinamide, an analog of nicotinamide, into pyrazinoic acid, which is a first-line drug against tuberculosis. Nicotinamidases are also regulators of intracellular nicotinamide concentrations, and hence participating in the signaling regulation of NAD+-consuming enzymes, such as sirtuins with NAD+-dependent deacetylase activity. Here, we report two high-resolution crystal structures of a nicotinamidase from a marine metagenomic microorganism in unligated form or covalently bound to the product nicotinic acid at 2.35 and 2.52 Å resolution, respectively. These structures provide detail about substrate binding, revealing several important features, including a metal ion that coordinates the substrate and the catalytically relevant water molecule. Comparison with known pyrazinamidase structures provides clues about the different selectivity of these closely related enzymes. The high activity reported by the biochemical analysis carried out reveals potential biotechnological implications of this metagenomic nicotinamidase.

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